PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P873PC00	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/DK2005/000176	International filing date *(day/month/year)* 16.03.2005	Priority date *(day/month/year)* 17.03.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K31/07 A61K31/05 A61P27/02		
Applicant LARSEN, Lars Michael		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 13 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 10 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.01.2006	26.06.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Bonzano, C Telephone No. +31 70 340-2202

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2005/000176

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-31	as originally filed
Claims, Numbers	
1-58	received on 17.01.2006 with letter of 17.01.2006
Drawings, Sheets	
1/3-3/3	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 1-58
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-26,53-65 (partially);48-50,52; 48-50,52; 58-61 (with regard to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 48-50,52; 58-61 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☒ no international search report has been established for the said claims Nos. 1-26,53-65 (partially); 48-50,52

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has, within the applicable time limit:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest and, where applicable, the protest fee.

   ☒ paid additional fees under protest but the applicable protest fee was not paid.

   ☐ neither restricted the claims nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-7,53-65 (partially), 8-47,51 .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	30-38,51
	No:	Claims	1-29,39-47,53-65
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-47,51,53-65
Industrial applicability (IA)	Yes:	Claims	1-47,51,53-57,62-65
	No:	Claims	58-61 (see separate sheet)

2. Citations and explanations (Rule 70.7):

   see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2005/000176

Amendments

1.1 The amendments filed with the letter dated 17.1.2006 introduce subject-matter which extends beyond the content of the application as filed, and are not allowable under Article 19(2) PCT and 34(2)b PCT. There is no base in the description to justify such amendments. The amendments concerned are in claim 1, where no disease treated is mentioned.

1.2 On the light of the letter of the applicant, it seems that the amendment wished is directed to the prevention of non-proliferative diabetic retinopathy. However, there is no basis in the application as originally filed for introducing such disorder in the claims: there is basis for introducing the disorders of original claims 4 and 6, namely diabetic retinopathy or retinopathy of prematurity, macular edema, angioproliferation, or neovascularization.
The disorder "non proliferative diabetic retinopathy" is mentioned in the description, page 1, line 29, only as background of the invention: moreover, it appears from the whole description that the invention is indeed directed to the treatment of proliferative diabetic retinopathy (see examples, where reference is made to neovascularisation, ischemia, vein occlusion and see the specific proliferative disorders of the eyes). The introduction of the disorder "non-proliferative retinopathy" in the letter represents an attempt to restore novelty over D7, without taking into consideration the original disclosure of the present application.
The amendments performed and intended by the applicant are therefore both not acceptable.

2. The present report is directed to the original set of claims 1-65 filed by the applicant.

Re Item III

1.1 Claims 1-6,53-65 encompass a genus of compounds defined only by their function, namely the activity as inhibitors of the visual cycle and/or dark adaptation, wherein the relationship between the structural features of the members of the genus and said function have not been defined. In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest using assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the

claimed activity.

1.2 Present claims 7-18,21-23,25,26,53-65 relate to an extremely large number of possible compounds (namely the compounds of formula I where R2 corresponds to formula II or formula III). Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. Moreover, the groups R3, R4 can be CH, which leaves the reader in doubt whether CH is connected with a double bond to the next carbon atom, or if it is just open to any possible attachement, multiplying the possibilities of compounds falling under formula I not being supported at all. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds as described in claims 19-20, those specifically mentioned in claim 24 and in claim 30.

1.3 Claims 1-3,5,7-24,53-61 relate to therapeutic applications which are actually not well defined. The use of the definitions "non-degenerative retinal disorder" or "disorder associated with diabetic retinopathy" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is not fully possible to determine the diseases for which protection might legitimately be sought. Therefore, the search has been performed only for the diseases listed in claims 4 and 6 (Articles 5, 6 PCT).
No report will be carried out in respect of subject-matter which is not covered by the search report (Rule 66(1)(e) PCT).

2. The subject matter of claims 58-61 concerns a method of treatment of the human/animal body which is considered by this Autorithy to be covered by the provisions of Rule 67.1 (IV) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims (Article 34(4) (a)(I)PCT).

Re Item IV.
An objection of lack of unity was raised in the search phase.
The separate groups of inventions are:

1a) 1-7,53-65 (partially), 8-24. Use for treating non-degenerative retinal disorders of a

compound capable of inhibiting the visual cycle and/or dark adaptation, namely a compound of formula I, where R2 corresponds to formula II.

1b) 1-7,53-65 (partially), 25-47,51. Use for treating non-degenerative retinal disorders of a compound capable of inhibiting the visual cycle and/or dark adaptation, namely a compound of formula I, where R2 is a substituted aryl of formula III or IV.

1c) 1-7,53-65 (partially). Use for treating non-degenerative retinal disorders of a compound capable of inhibiting the visual cycle and/or dark adaptation, namely a compound of formula I, where R2 is a substituted heteroaryl of formula III or IV.

1d) 1-7,53-65 (partially), 48-50. Use for treating non-degenerative retinal disorders of a compound capable of inhibiting the visual cycle and/or dark adaptation, namely a compound of formula I, where R2 is oxygen.

2) 1-7,53-65 (partially), 52. Use for treating non-degenerative retinal disorders of a compound capable of inhibiting the visual cycle and/or dark adaptation, namely the compound DAPP.

The inventions 1) and 2) are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons. The problem to be solved by the present invention is to provide a medicament for treating non-degenerative retinal disorders. The proposed solution is to use a compound capable of inhibiting the visual cycle and/or dark adaptation, in particular a compound of formula I.
The activity as inhibitors of the visual cycle and/or dark adaptation represents the technical feature common to these (structurally) different compounds and to the different compositions claimed.

The document WO03004058 (D1) cited in the search report discloses the use of α 1-adrenergic receptor blockers for protecting optic nerves and for treating retinal diseases such as normotensive glaucoma, retinal vein occlusion, diabetic retinopathy, ischemic optic neuropathy, macular degeneration, retinitis pigmentosa and Leber's disease (see abstract). The active ingredients of the present document are compounds capable of inhibiting the visual cycle and/or dark adaptation: see EP0522226 (D2), page 2, lines 11-15 "α blockers and pilocarpine induce miosis and therefore reduce visual capacity and dark adaptation".
Consequently, because inhibitors of the visual cycle and/or dark adaptation, as claimed, have already been used in the treatment of retinopathy, the activity as inhibitors of the visual cycle

and/or dark adaptation can no longer serve as a single general inventive concept linking the compounds of claim 7, to the compound DAPP, which have no other technical feature in common, in particular:
1) the compounds of formula I where R2 corresponds to formula II, or R2 is a substituted aryl of formula III or IV or R2 is a substituted heteroaryl of formula III or IV or R2 is O;
2) the compound DAPP.
Therefore the uses of the compounds 1) and 2) in the treatment of non degenerative retinal disorders represent each a distinct invention, characterised by its own special technical features, i.e. the structural features of the compounds.
The documents cited above do not represent a comprehensive search for the defined inventions and are to be considered in the present context only as part of the prior art pertaining to the general idea underlying the present application.
An objection of lack of unity was raised in the search phase between the inventions 1a), 1b), 1c), 1d) and 2).
One additional fee was paid under protest by the applicant in the search phase: a search was performed only on inventions 1a) and 1b), which were recognised by the search authority as unitary. Therefore, the fee was refunded to the applicant. The present report refers only to unitary matter for which a search was performed, namely the compounds of formula I, where R2 corresponds to formula II and formula III, for treating the disorders of claims 4 and 6: claims 1-7,53-65 (partially), 8-47,51. No report is being performed on claims 48-50,52.
No report will be performed on the other inventions, which were not searched.

Re Item V.

1. Reference is made to the following documents:
   - D1 : WO 03/004058 A (SANTEN PHARMACEUTICAL CO., LTD; EISAI CO., LTD; MIYAWAKI, NOBUAKI; HAR) 16 January 2003 (2003-01-16)
   - D2: EP 0 522 226 A (COSTAGLIOLA, CIRO) 13 January 1993 (1993-01-13)
   - D3: US 2003/032078 A1 (TRAVIS GABRIEL H) 13 February 2003 (2003-02-13)
   - D4 : WROBEL A ET AL: "Antiangiogenic activity of agonist and antagonists of retinoid nuclear receptors" PRZEGLAD DERMATOLOGICZNY 1999 POLAND, vol. 86, no. 4, 1999, pages 339-346, XP000879096 ISSN: 0033-2526
   - D5: MARMOR M F ET AL: "Albipunctate retinopathy with cone dysfunction and no abnormality in the RDH5 or RLBP1 genes" RETINA 2003 UNITED STATES, vol. 23, no. 4, 2003, pages 543-546, XP008049556

D6: OIKAWA T ET AL: "THREE NOVEL SYNTHETIC RETINOIDS, RE 80, AM 580 AND AM 80, ALL EXHIBIT ANTI-ANGIOGENIC ACTIVITY IN VIVO" EUROPEAN JOURNAL OF PHARMACOLOGY, AMSTERDAM, NL, vol. 249, no. 1, November 1993 (1993-11), pages 113-116, XP000879175 ISSN: 0014-2999

D7: US-A-5 824 685 (CAMPOCHIARO ET AL) 20 October 1998 (1998-10-20)

2. The applicant attention is drawn to the fact that the present report expressed as to novelty, inventive step and industrial applicability refers only to matter for which an international search report has been drawn up and for which additional fees have been paid (i.e. the compounds of formula I, where R2 corresponds to formula II and formula III, for treating the disorders of claims 4 and 6).

3. For the assessment of the present claims 58-61 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Novelty

4.1 The document D1 discloses the use of α 1-adrenergic receptor blockers for protecting optic nerves and for treating retinal diseases such as normotensive glaucoma, retinal vein occlusion, diabetic retinopathy, ischemic optic neuropathy, macular degeneration, retinitis pigmentosa and Leber's disease (see abstract).
The active ingredients of the present document are compounds capable of inhibiting the visual cycle and/or dark adaptation: see D2, page 2, lines 11-15 "α blockers and pilocarpine induce miosis and therefore reduce visual capacity and dark adaptation".
The subject-matter of claims 1-6,53-65 is therefore not new over D1 (Article 33(2) PCT).

4.2 D4 discloses the antiangiogenic compounds retinoids as being useful in the treatments of pathologies such as diabetic retinopathy: the retinoids seem to be RO482249 and RO479240 (cd2665 is not a retinoid).
The subject-matter of claims 1-6,53-65 is therefore not new over D4 (Article 33(2) PCT).

4.3 D6 discloses the compound A of figure 1 (Re 80) corresponding to formula VII, described in claim 27, (the tautomer of the compound Re80, it corresponds to claim 27): it is useful for treating diabetic retinopathy, the disease of claim 4.
The subject-matter of claims 1-5,7, 25-27 is therefore not new over D6 (Article 33(2) PCT).

4.4 D7 discloses compounds according to invention I (all trans RA; 13 cis RA, which is isotretinoin, according to claim 24) and to invention II (compound 183 corresponding to formula VII, claim 27; and compound 121 corresponding to formula IX, claim 39) for treating proliferative vitreoretinopathy, severe scarring occurring in association with macular degeneration, poor recovery of vision after retinal reattachment.
In advanced diabetic retinopathy, a proliferative, angiogenic response with retinal neovascularization occurs, placing the eye at risk for severe visual loss because of the development of vitreous hemorrhage or traction retinal detachment: **nonproliferative retinopathy** is the earlier stage. In this stage there may be hemorrhages (bleeding) in the retina with leakage of blood causing a "wet retina" or protein deposits (exudates) in the retina. As a consequence, the retina does not receive enough oxygen. This early stage of diabetic retinopathy usually produces no visual symptoms but, if there is fluid in the central portion of the eye (macular edema), vision is diminished. **Proliferative retinopathy** is the second stage. New abnormal vessels develop in the retina and grow towards the center of the eye. These vessels frequently **bleed into the vitreous** (the clear jelly in the center of the eye). Such bleeding episodes cause severe visual problems. Small bleeds may clear up on their own but larger bleeds need surgery. The abnormal vessels may also produce large scars in the retina that may cause the underlying retina to **detach (retinal detachment)**: see definitions of the medical dictionary.
Proliferative vitreoretinopathy (the disease disclosed in D7) is the leading cause of failure of retinal reattachment surgery. This disorder is associated with the development of proliferative epiretinal membranes that contract on the surface of and under the retina, resulting in recurrent **retinal detachment**.
There is therefore a clear overlap between the diseases treated in D7 and diabetic retinopathy treated in the present application.
In the absence of a distinction between the presently claimed disorders and the disorders of D7, novelty cannot be aknowledged for claims 1-29, 39-47, 53-65 over D7 under Article 33(2) PCT.

Inventive step

5.1 The subject matter of present claims 30-38,51 appears to be novel and meets therefore the requirements of Article 33(2) PCT. None of the prior art documents discloses the use of the compounds of claims 30-38 and 51 for treating the disorders of claims 4 and 6. The present application however does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1-29,39-47,53-65, as far as novel, and 30-38,51 does not involve an inventive step.

Document D4, which is considered to represent the most relevant state of the art, discloses the antiangiogenic compounds retinoids as being useful in the treatments of pathologies such as diabetic retinopathy: the retinoids seem to be RO482249 and RO479240.

The present application differs in that the same diseases are treated in the same patients using different retinoid derivatives.

The problem to be solved by the present invention may therefore be regarded as finding an alternative treatment to diabetic retinopathy.

Document D3 discloses compounds of formula I, falling under the first invention, such as trans-retinaldheyde, all-trans RAL, (see figure 6) for treating macular and retinal degenerations, explicitely disclaimed in the present application.

Therefore, being aware that the claimed compounds are useful for treating degenerative macular disorders, and knowing that similar retinoids are used for treating the claimed non degenerative macular disorders, such as diabetic retinopathy, the person skilled in the art would have been inevitably led to use the compounds of the present invention for treating also non degenerative macular disorders.

5.2 Moreover, D5 discloses that 11-cis-retinol, 11-cis retinaldheyde are produced in the conjunctiva and that they are necessary for the function of retinal epithelium: the alteration of their synthesis is responsible for prolongation of dark adaptation and night blindness. This teaching would strenghthen the motivation of the man skilled in the art to use them for improving retinal and conjunctival function.

The subject-matter of claims 1-29,39-47,53-65, as far as novel, and 30-38,51 does not involve an inventive step (Article 33(3) PCT).

5.3 D7 discloses compounds according to invention 1a (all trans RA; 13 cis RA, which is isotretinoin, according to claim 24) and to invention 1b (compound 183 corresponding to formula VII, claim 27; and compound 121 corresponding to formula IX, claim 39) for treating

proliferative vitreoretinopathy, severe scarring occurring in association with macular degeneration, poor recovery of vision after retinal reattachment.

The present application differs in that the same groups of compounds are used for treating non degenerative retinal disorders, in particular diabetic retinopathy.

It would be obvious for the man skilled in the art to use the compounds of D7 for treating diabetic retinopathy, knowing that they are useful for treating vitreoretinopathy and poor recovery of vision after retinal reattachment. In particular, the knowledge that diabetic retinopathy places the eye at risk for severe visual loss because of the development of vitreous hemorrhage or traction retinal detachment, which are the symptoms of vitreoretinopathy too, would inevitably lead the man skilled in the art to expect from these compounds an activity against diabetic retinopathy, as well as against vitreoretinopathy as disclosed in D7.

The subject-matter of claims 1-29,39-47,53-65, as far as novel, and 30-38,51 does not involve an inventive step under Article 33(3) PCT.

PCT/DK2005/000176
Representativs Ref. P873PC00

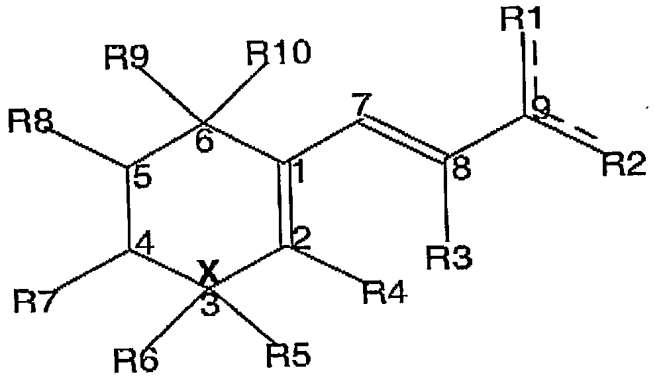
Claims

1. Use of at least one compound capable of inhibiting the visual cycle in an individual in the manufacture of a medicament for prevention or treatment of, in a mammal.

2. Use according to claim 1, wherein said mammal is a human being.

3. Use according to any of claims 1 and 2, wherein said mammal has been diagnosed with diabetes.

4. Use according to any of the preceding claims, wherein the at least one compound comprises a compound of the formula I:

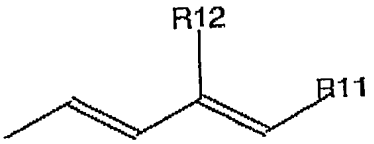


(formula I)

wherein R1 is:

- a lower alkyl, preferably CH2CH3 or CH3, having a single bond to the carbon at position 9 (C9), wherein the bond between C9 and R2 preferably is a double bond, or
- CH2OH or CHO or CF3, or
- CH2 with a double bond to C9, or
- a bond from C9 to R2, or
- OH

and wherein R2 is:



(formula II)

wherein R11 is selected from the group consisting of:

- an alcohol group, such as -CH2OH,
- an aldehyde group, such as -CHO,
- carboxy (-COOH),
- a lower alkyl group, such as -CH3,
- an ether group, such as -CH2OCH3, -CH2OC4H9, -CH2OC6H5 or -CH2OC8H17,
- an ester group, such as -CH2OCOCH3,
- a amine derivative, such as -CH2NHCOCH3, -CH2NHCOC6H5, or -CH2NCH3COCH3,

-CH3COC6H5,
-CH=NOH,
-CH=NNHCOCH3,
-CH=C(COCH2CH2CH3)2,
-CH=C(COCH2)2,
-CH=C(COCH2)2CH2CH=C(COCH2CH2)2CH2,
-COOCH3,
-COOCH2H5,
-COZ, wherein Z is an amino acid, such as glycine, leucine, phenylalanine, or tyrosine,
-CONHC2H5,
-CONHC3H7,
-CONH2C2H4OH,
-CONH2C3H6OH,
-CONH3C3H6OH,
-CONHC6H5,
-CONH2C6H4OH,
-CONH4C6H4OH,
-CONH2C6H4COOH,
-CONH4C6H4COOH,
-CH2OCOCH2Br,

-CH2OCOCH2Cl,

-COOCH2CH3,

- an N-alkylamide group, such as -CONHR, wherein R is an alkyl, preferably 4-hydroxy-phenyl or ethyl,

-COOR, wherein R is beta-D-glucuronide,

- an ethyl sulfone group,

- an ethyl ester group, and

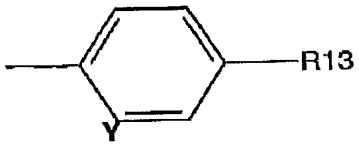
- an alkoxycarbonyl group, such as ethoxycarbonyl

and wherein R12 is:

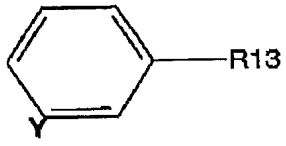
- a lower alkyl, preferably CH3 or CH2CH3, or

- CH2OH or CHO or CF3,

or R2 is a substituted aryl or heteroaryl, such as:



(formula III) or



(formula IV)

wherein R13 is selected from the group consisting of:

- carboxy (-COOH),

- an alcohol group, such as -CH2OH,

- an aldehyde group, such as –CHO,

-CH2OCOCH2Br,

-CH2OCOCH2Cl,

-COOCH2CH3,

- a CONHR group, wherein R is an alkyl, preferably 4-hydroxy-phenyl or ethyl),

- COOR, wherein R is beta-D-glucuronide,

- an ethyl sulfone group,

- an ethyl ester group, and

- an alkoxycarbonyl group, such as ethoxycarbonyl;

and wherein Y is C or N or S or O

or R2 is

- O, having a double bond to C9

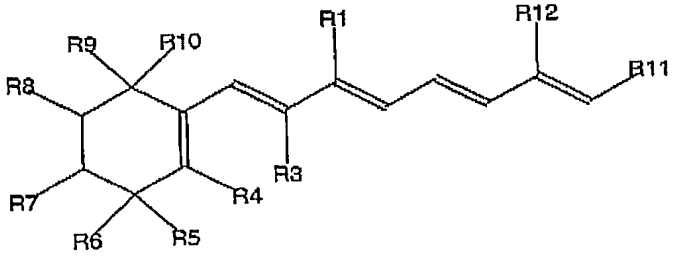
wherein R3 is OH or a lower alkyl or H or CH or CHRCH3 (wherein R is a double bond to R4),
and wherein R4 is H or CH or OH or a lower alkyl, such as CH3,
and wherein R5 is OH or a lower alkyl, such as CH3, or H or O (double bond to atom at position 3) or absent,
and wherein R6 is OH or a lower alkyl, such as CH3, or H or absent or a bond to R5 (if R5 is O) or a bond to C4,
and wherein R7 is alkoxy, such as methoxy, or OH or a lower alkyl, such as CH3, or H or 3-(1-adamantyl)-4-methoxyphenyl,
and wherein R8 is OH or a lower alkyl, such as CH3, or H or a bond to C6,
and wherein R9 is OH or a lower alkyl, such as CH3, or H,
and wherein R10 is OH or a lower alkyl, such as CH3, or H or a bond to C5,
and wherein X is C or N or S or O.

and wherein each of R1, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12 and R13, is optionally substituted one or more times with a lower alkyl group, such as a methyl group or an ethyl group,

with the proviso that when R2 is formula II, and R1, R4, R9 and R12 are all CH3, and R3, R5, R6, R7 and R8 are all H and R11 is a carboxy group, the configuration is not 9-cis (2E,4E,6Z,8E) or all-trans,

and the proviso that when R2 is formula II, and R1, R4, R9 and R12 are all CH3, and R3, R5, R6, R7 and R8 are all H and R11 is an alcohol group, the configuration is not all-trans.

5. Use according to claim 1 or 4, wherein the at least one compound comprises a retinoid, preferably a compound of the formula V:



(formula V)

wherein the configuration of the four isoprenoid units is all trans (E) or one or more is cis (Z).

6. The use of claim 5, wherein the configurations around the carbon-carbon double bands are all-trans (2E,4E,6E,8E) or 9-cis (2E,4E,6Z,8E), or 11-cis (2E,4Z,6E,8E), or 13-cis (2Z,4E,6E,8E).

7. The use of claim 5 or 6, wherein R3 is H.

8. The use of any of claims 5 to 7, wherein R4 is CH3.

9. The use of any of claims5 to 8, wherein R5 is H.

10. The use of any of claims 5 to 9, wherein R6 is H.

11. The use of any of claims 5 to 10, wherein R7 is H.

12. The use of any of claims 5 to 11, wherein R8 is H.

13. The use of any of claims 5 to 12, wherein R9 is CH3.

14. The use of any of claims 5 to 13, wherein R10 is CH3.

15. The use of claim 5, wherein R5 is O and R6 is a bond to R5.

16. The use of claim 5, wherein R3 is H and R4 is CH3, and R5 is O and R6 is a bond to R5, and R7 is H, and R8 is H, and R9 is CH3, and R10 is CH3.

17. The use of claim 5, wherein R3 is H, and R4 is CH3, and R5 is H, and R6 is H, and R7 is methoxy, and R8 is CH3, and R9 is CH3, and R10 is H.

18. The use of any of claims 5 to 17, wherein R11 is selected from the group consisting of:

-COOH,

- an alcohol group, such as -CH2OH,

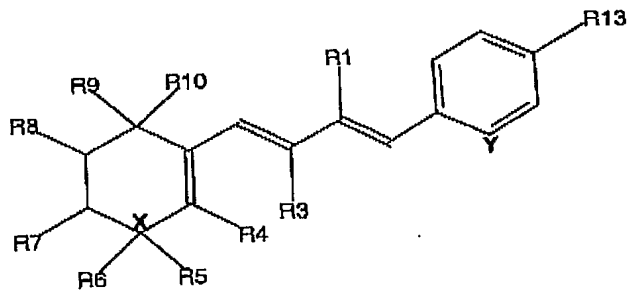
- an aldehyde group, such as -CHO,
-CH2OCOCH2Br,
-CH2OCOCH2Cl,
-COOCH2CH3,
-CONHR, wherein R is preferably 4-hydroxy-phenyl or ethyl, and
-COOR, wherein R is beta-D-glucuronide.

19. The use of any of claims 5 to 18, wherein R1 is CH3.

20. The use of any of claims 5 to 19, wherein R12 is CH3.

21. The use of claim 1 or 5, wherein the at least one compound comprises a compound selected from the group consisting of: isotretinoin (13-*cis*-retinoic acid), 11-*cis*-retinol, 11-*cis*-retinal, 11-*cis*-retinyl bromoacetate, acitretin, etretinate, fenretinide, 4-oxo-isotretinoin, motretinide, retinaldehyde, *all-trans*-retinyl bromoacetate, *all-trans*-retinyl chloroacetate, and retinoyl betaglucoronide.

22. The use of claim 4, where the compound has the formula VI:

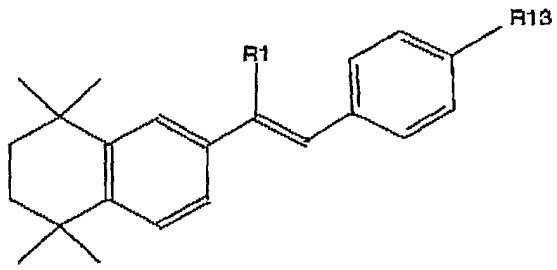


(formula VI)

23. The use of claim 22, wherein R3 and R4 are both CH and are connected by a double bond.

24. The use of claim 23, wherein the compound has the formula VII:

7



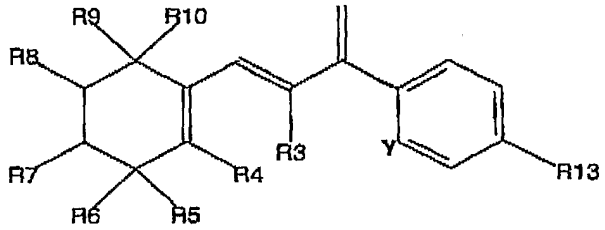
(formula VII)

25. The use of claim 24, wherein R13 is selected from the group consisting of: a carboxy (COOH) group, an ethyl sulfone group, and an ethyl ester group.

26. The use of claim 24 or 25, wherein R1 is CH3.

27. The use of claim 1 or 24, wherein the at least one compound comprises a compound selected from the group consisting of: arotinoid ethyl ester, arotinoid-free carboxylic acid and arotinoid ethyl sulfone.

28. The use of claim 4, wherein the at least one compound has the formula VIII:



(formula VIII)

29. The use of claim 28, wherein R3 and R4 are both CH and are connected by a double bond.

30. The use of claim 28, wherein R4 is CH and R3 is CHRCH3, wherein R is a double bond to R4.

31. The use of any of claims 28 to 30, wherein one or more, preferably all, of R5, R6, R9 and R10 are CH3.

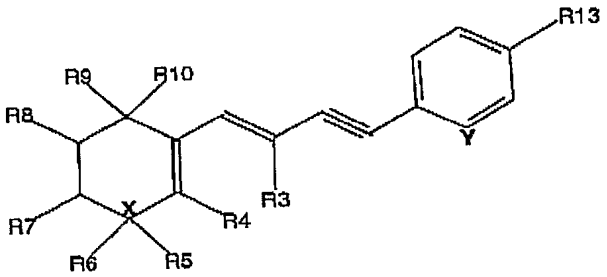
32. The use of any of claims 28 to 31, wherein R7 and R8 are both H.

33. The use of any of claims 28 to 32, wherein Y is C.

34. The use of any of claims 28 to 33, wherein R13 is a carboxy group.

35. The use of claim 1 or 28, wherein the at least one compound comprises bexarotene.

36. The use of claim 4, wherein the at least one compound comprises a compound of the formula IX:



(formula IX)

37. The use of claim 36, wherein R3 and R4 are both CH and form a double bond.

38. The use of claim 36, wherein R4 is CH and R3 is CHRCH3, wherein R is a double bond to R4.

39. The use of any of claims 36 to 38, wherein R9 and R10 are both CH3.

40. The use of any of claims 36 to 39, wherein R7 and R8 are both H.

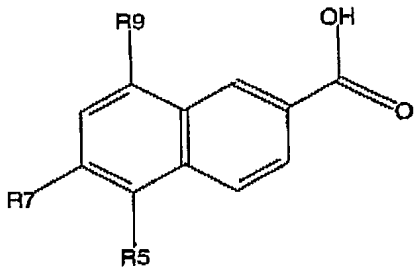
41. The use of any of claims 36 to 40, wherein X is S and R5 and R6 are absent.

42. The use of any of claims 36 to 41, wherein Y is N.

43. The use of any of claims 36 to 42, wherein R13 is a alkoxycarbonyl group, preferably an ethoxycarbonyl group.

44. The use of claim 1 or 36, wherein the at least one compound comprises tazarotene.

45. The use of claim 4, wherein the at least one compound comprises a compound of the formula X:



(formula X)

46. The use of claim 45, wherein R5 is H and R9 is H.

47. The use of claim 45 or 46, wherein R7 is 3-(1-adamantyl)-4-methoxyphenyl.

48. The use of claim 1 or 45, wherein the at least one compound comprises adapalene.

49. The use of any of claims 1 to 3, wherein the at least one compound is DAPP.

50. Use according to any of the preceding claims, wherein the at least one compound is composed as a pro-drug.

51. Use according to any of the preceding claims, wherein the medicament is in a form for being administered locally.

52. Use according to claim 51, wherein the medicament is in a form for being administered intravitreally.

53. Use according to any of the preceding claims, wherein the medicament is in device formulation held confined by mechanical or physico-chemical effects.

54. Use according to any of the preceding claims, wherein the medicament is in a slow-release formulation.

55. A pharmaceutical composition suitable for intravitreal implantation comprising a pharmaceutically effective amount of at least one compound capable of inhibiting the visual cycle and/or dark adaptation.

56. The pharmaceutical composition of claim 55, wherein said pharmaceutically effective amount of said at least one compound is determined by measuring the level of reduction of dark adaptation in a treated subject.

57. The pharmaceutical composition of claim 55 or 56, wherein said pharmaceutical composition is in device formulation held confined by physico-chemical effects.

58. The pharmaceutical composition of any of claims 55 to 57, wherein said at least one compound comprises a compound having at least one feature according to any of claims 2 to 54.